Fertility and exposure to solvents among families in the Agricultural Health Study

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Occup. Environ. Med. 2006;63;469-475; originally published online 12 May 2006;
doi:10.1136/oem.2005.021337

ORIGINAL ARTICLE

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Occup Environ Med 2006;**63**:469–475. doi: 10.1136/oem.2005.021337

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Accepted 22 February 2006
Published Online First 12 May 2006

Background: Several studies have reported associations between solvent exposure and reduced female fertility, but the evidence is inconclusive for male fertility.
Objectives: To investigate the impact of solvent exposure on subfertility among families of male licensed pesticide applicators in the Agricultural Health Study cohort.
Methods: The couples enrolled between 1993 and 1997. Cross-sectional questionnaire information on work tasks was used to assess exposure to solvents. The data were limited to couples (wife aged less than 40 years) with an attempt at pregnancy in the last four years (n = 2112).
Results: Twenty eight per cent of the couples were defined as subfertile (not conceiving a pregnancy after at least 12 months of unprotected intercourse, regardless of whether or not a pregnancy ultimately occurred). Adjusted subfertility odds ratios (OR) for exposure to solvents were calculated with logistic regression. Female (OR 1.42, 95% CI 1.15 to 1.75) and male exposure to solvents (OR 1.21 (95% CI 0.93 to 1.57) for monthly exposure and 1.40 (95% CI 0.97 to 2.03) for daily or weekly exposure) were associated with subfertility. In farming, spouses may share or exchange jobs. To account for potential dual exposure, variables for parental exposure (either parent exposed or both parents exposed) were also defined. Both were strongly associated with subfertility (OR 1.62 (95% CI 1.20 to 2.17) and OR 2.10 (95% CI 1.22 to 3.60), respectively).
Conclusions: Solvents may impair fertility of either gender, though the evidence for female effects is stronger than for male effects.

There are several lines of evidence that suggest solvents could contribute to reduced fertility, particularly in women. Organic solvents are volatile liquids that enter the human body easily through inhalation or skin absorption. Solvents or their metabolites are rapidly distributed through the circulation to different tissues. Reproductive disorders including menstrual and fertility problems and spontaneous abortion have been associated with exposures.[1 2] In animal experiments, ethylene glycol ethers,[3] *n*-hexane,[4] and thinners, particularly the components ethyl acetate and xylene,[5] can cause testicular damage and degeneration. Complex interactions have also been reported. For example, simultaneous exposure to toluene and xylene was found to protect rats from testicular atrophy induced by either *n*-hexane[4] or ethylene glycol monoethyl ether.[3] Semen studies of solvent exposed workers have also shown adverse effects of ethylene glycol ethers and their acetates, and carbon disulphide.[6–8] Data on the associations between exposure to solvents and reduced fertility as measured by prolonged times to conception are fairly consistent for female exposure, but inconclusive for male exposure.[9] Different solvents may have different mechanisms of action through which they can cause reduced fertility. For example, glycol ethers are proposed to act through genetic or epigenetic mechanisms or alterations in gene regulation. These pathways may lead to cell apoptosis, cell cycle arrest, or cell transformation, leading to reduced fertility.[10]

The aim of the present study was to investigate fertility effects of solvent exposure among farm families in the Agricultural Health Study (AHS) cohort.[11] The AHS offers a good opportunity to focus on the impact of solvent exposure on reproductive outcomes because of large sample size and high prevalence of exposure.

SUBJECT AND METHODS

Study population and data collection

Fertility was evaluated among the families in the Agricultural Health Study (AHS) cohort. The AHS is composed of certified pesticide applicators in Iowa and North Carolina and their spouses.[11] Approximately 51 000 male private applicators (largely farmers) and 1300 female applicators in Iowa and North Carolina enrolled at pesticide certification by completing the enrolment questionnaire between 1993 and 1997. About 75% of eligible spouses enrolled (n = 32 347) by completing an exposure questionnaire by mail or telephone. The study protocol was approved by the Human Subject's Review Boards of each collaborating agency and informed consent was obtained from study participants prior to data collection.

For the present study, beginning with the 32 347 applicator–spouse pairs, we excluded the families in which the woman was the applicator (91 of them would have fulfilled the eligibility criteria shown below) because the core questions on exposure differed for applicators and spouses, making it difficult to categorise exposures in the same way. Among the male applicator–spouse pairs, 19 579 of the spouses provided data on reproductive history by completing the Female and Family Health Questionnaire. We further restricted our analysis to premenopausal women aged <40 years at the time of data collection to coincide with child bearing years and partially control for older age, a major risk factor for reduced fertility. Approximately 70% of the wives were aged 40 years or older, leaving us with 5526 couples potentially at risk for pregnancy during the study period (see below).

Like the other baseline questionnaires in the AHS, the Female and Family Health Questionnaire was

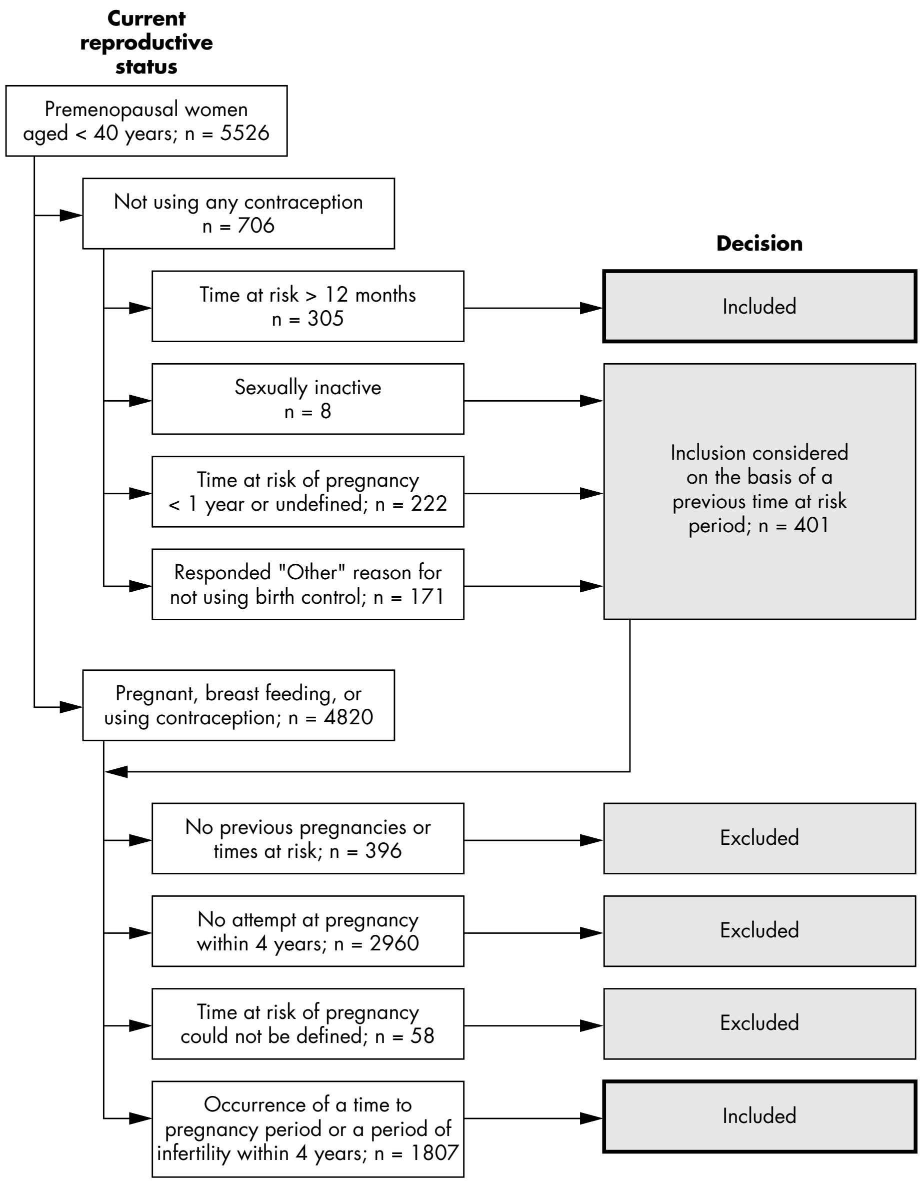

Figure 1 The inclusion of subjects into the study according to current reproductive status and reproductive history in a study among farmers and their wives in the Agricultural Health Study. (1) Couples who currently had been >12 months without using any contraception were included as subfertile (n = 305). For all the others, inclusion was considered on the basis of having at risk time within four years of enrolment. These included (2) those who currently were not at risk of getting pregnant, i.e. pregnant, breast feeding, or using contraception (n = 4820), and (3) those for whom fertility status could not be defined reliably (n = 401).

self-administered, and designed to be scanned (AHS questionnaire available at www.aghealth.org), making it necessary to include categorical response categories. It included questions about birth control, infertility, and pregnancy history. Subfertility was defined as taking more than 12 months to conceive, regardless of whether or not a pregnancy ultimately was achieved. Responses that reflected a subfertility or infertility history were: "tried >12 months since last pregnancy", "tried >12 months for a prior pregnancy", "never pregnant but tried >12 months", and "ever used fertility drugs". The focus of our analysis was on the most recent time to pregnancy (TTP) or period of infertility to be as concurrent as possible with the exposure data. We could clearly ascertain the fertility status of the most recent attempt for those who answered no to all of the subfertility/infertility questions and for those subjects with a history of infertility who had never been pregnant but had tried, had tried after their last pregnancy, or had only one pregnancy. However, ascertainment for multigravid women was more complicated because women were not asked time to pregnancy for each pregnancy; rather they were asked if they ever took more than 12 months to conceive. Therefore, multigravid women who reported ever taking >12 months to conceive a prior pregnancy were assumed to have experienced a period of subfertility with their last pregnancy if the non-pregnant interval before their last pregnancy was sufficiently long (at least 16 months after a birth and at least 14 months after a loss).

Current reproductive status of each woman was defined as follows: (1) using oral contraceptives (n = 1287); (2) pregnant or breast feeding (n = 537); (3) using other methods of birth control (n = 2680; including tubal ligation and vasectomy); (4) at risk of pregnancy (n = 706), i.e. those who reported that they were currently not using any method of birth control; and (5) missing information on items 3 and 4 above (n = 316). Women at risk of pregnancy were asked how long it had been since they had used birth control (response categories: ''this month'', ''last month'', ''2–5 months ago'', ''6–12 months ago'', ''>12 months ago'', and ''have not used birth control'') and their primary reason for not using birth control (response categories: ''trying to become pregnant'', ''OK to become pregnant'', ''don't think I can become pregnant'', ''stopped one method of birth control and haven't started another'', ''just don't use birth control methods'', and ''other reason'').

In the present study we followed the occurrence of the health outcome from a specified calendar time onwards.[12 13] In this study time 0 is four years before data collection. Eligible participants were couples who had had a TTP period or a period of subfertility estimated to have started no more than four years before data collection. The inclusion of couples was based on the estimated start of a pregnancy attempt, and not on the dates of pregnancies in order to maintain similar distributions between fertile and subfertile couples for the start times of their pregnancy attempts. The AHS questions focused on the usual exposure and behaviour of couples at the time of enrolment. The selected design allowed us to obtain comparable information on exposure and potential confounders for the fertile and subfertile couples during the at risk period. We selected a four year study period to increase study size and limit misclassification of exposure that would increase if recall covered a longer time period.

Inclusion of the subjects into the study is presented in fig 1. Women currently at risk of pregnancy were included if they had been at risk for more than 12 months and the reason for not using birth control was any response except ''other reason'' (n = 305). It was not clear that the 171 subjects who reported ''other reason'' were really at risk of pregnancy, so this group was evaluated on the basis of any previous time at risk (see below), but findings were checked and found to be similar if the 171 were treated as currently at risk.

In addition to the 305 women noted above, the remaining 5221 subjects (including the 171 subjects above, couples having currently been at risk of pregnancy for less than a year (n = 214), unknown time at risk (n = 8), and sexually inactive couples (n = 8)) were included in the analysis if they had either a successful or unsuccessful pregnancy attempt estimated to have occurred within the four year interval of interest (see fig 1). In order to estimate the start of an attempt we assigned subfertile couples an attempt time of 18 months and fertile couples an attempt time of 3 months. For example, a subfertile couple with a pregnancy ending 24 months before data collection would have been excluded because their attempt would have been estimated to start before the four year window (24 months + 9 months for the pregnancy + 18 months for the attempt time = 51 months before data collection). This criterion resulted in 3414 exclusions (396 couples with no previous pregnancies or prolonged pregnancy attempts, 2960 couples with previous pregnancies, but all attempts to conceive had begun before the four year interval, and 58 couples with a previous attempt for which we could not determine whether the attempt had likely started during the four year interval). Thus, our final study population consisted of 2112 subjects. Most of the exclusions (n = 3356) among the 5526 women were because of lack of time to pregnancies or times at risk within the four year study period.

Exposure assessment

Female and male exposure to solvents was based on questions about work tasks. Female exposure to solvents was defined as doing the following home or work activities at least once a month: painting or using gasoline or other solvents (like paint stripper, turpentine, benzene) for cleaning hands or equipment. There were separate questions for summer and winter season. Wives were defined as exposed if they answered ''yes'' to any of these questions in either season. Wives were classified as unexposed if they answered ''no'' to all these questions. For men, the questions on solvent exposure also included the frequency of the activities. Men's exposure was ranked ''daily or weekly'' if any of the work tasks was done daily (6–7 times a week) or weekly (1–5 times a week) and ''monthly'' if any solvent activities were done only monthly (1–3 times a month). An unexposed or minimally exposed reference group consisted of men who reported a frequency of ''never or less than once a month'' for solvent use. Parental exposure was defined as exposure of either the applicator or his spouse. We also examined parental exposure defining separate variables for female exposure, male exposure, and female and male exposure. Female, male, and parental exposures were considered as missing if all the solvent questions were unanswered. Solvent exposure was missing for 33 women, and 619 men because the information for solvent related work tasks was asked in the Farmer Applicator Questionnaire and not in the Enrolment Questionnaire, and some participants did not complete this questionnaire.

Statistical analysis

Data on subfertility were analysed by logistic regression. The outcome parameter is the subfertility odds ratio (OR); ORs above unity reflect increased subfertility, i.e. reduced fertility. Potential confounders considered were age, body mass index (BMI, in kg/m^2; calculated as weight in kilograms divided by height squared in metres), smoking, use of alcohol, exposure to pesticides, and male welding. Information on these variables was obtained at the time of baseline data collection. Age at estimated start of pregnancy attempt was calculated and used in analysis. Our analysis assumes that values for factors used in the analysis were not substantially different at TTP from that reported at time of data collection. The ORs were also adjusted for state (Iowa or North Carolina) of residence. In the multivariate model, wife's use of alcohol and male welding and smoking were not statistically significantly associated with subfertility, and the inclusion of these variables had little effect on the association between subfertility and female or male solvent exposure. The solvent associations did not change when adjusted for male and/or female exposure to pesticides overall or exposure to specific functional or chemical classes of pesticides. Thus, these variables were not included in the final multivariate model.

RESULTS

Twenty eight per cent of the couples were defined as subfertile. Distribution of potential confounders and prevalence of subfertility are shown in table 1. As expected, subfertility increases with female age, body mass index, and smoking. Male use of alcohol was related to better fertility. Female exposure to solvents was associated with subfertility in both crude and adjusted analyses (adjusted subfertility odds ratio (OR) 1.42, 95% CI 1.15 to 1.76) (table 2). Male exposure to solvents was also related to reduced fertility (table 2). The association showed a dose-response pattern (adjusted OR 1.41, 95% CI 0.98 to 2.05 for high exposure). Parental exposure (exposure of either the applicator or his spouse) was also associated with reduced fertility (adjusted OR 1.62, 95% CI 1.20 to 2.17). The strongest association was seen in families where both man and wife were exposed (adjusted OR for simultaneous female exposure and male high exposure 2.10, 95% CI 1.22 to 3.60).

Table 1 Exposure to potential confounding factors and prevalence of subfertility among farmers and their wives from the Agricultural Health Study, United States, 1993–97

	Female		Male	
Exposure	**No.**	**% subfertile**	**No.**	**% subfertile**
Age				
<25 years	305	20.7	123	28.5
25–29 years	788	19.8	586	18.8
30–34 years	765	31.4	803	26.0
35–39 years	254	52.4	468	37.8
40–54 years	0*		132	46.2
Body mass index (BMI, in kg/m^2)				
⩽19	223	24.7	32	21.9
20–24	898	26.2	447	24.6
25–29	434	26.5	710	27.9
30–44	241	39.4	279	37.6
Missing	316	29.1	644†	26.7
Smoking				
Never smoked	1584	25.8	1485	26.5
Current smoker	163	43.6	252	34.5
Ex-smoker	297	30.0	329	28.6
Missing	68	33.8	46	37.0
Use of alcohol (drinks per month during the past 12 months)				
Non-user	696	30.2	417	33.6
<3	734	25.5	347	30.3
3–8	477	26.6	605	25.3
9–26	121	28.1	358	23.2
⩾27	46	37.0	307	27.7
Missing	38	44.7	78	33.3
Welding				
Not exposed or less than once a month			326	28.2
Monthly			713	28.3
Daily or weekly			451	29.9
Missing			622†	26.2
State				
Iowa	1651	27.8		
North Carolina	461	33.0		

*Excluded in defining the sample.
†Question not included in the enrolment questionnaire.

Table 2 Unadjusted and adjusted subfertility odds ratios (OR) for exposure to solvents among farmers and their wives from the Agricultural Health Study, United States, 1993–97; three unadjusted and three adjusted logistic regression models

		Unadjusted*		Adjusted*	
Exposure	**No.**	**OR**	**95% CI**	**OR**	**95% CI**
Model 1					
Female exposure to solvents (at least once a month)					
No	1322	1.00	ref.	1.00	ref.
Yes	757	1.27	1.04 to 1.55	1.42	1.15 to 1.76
Male exposure to solvents					
No or less than once a month	524	1.00	ref.	1.00	ref.
Monthly	761	1.13	0.88 to 1.45	1.21	0.93 to 1.57
Daily or weekly	208	1.36	0.96 to 1.93	1.41	0.98 to 2.05
Model 2					
Parental exposure to solvents					
Neither parent exposed	347	1.00	ref.	1.00	ref.
Either parent exposed	1341	1.39	1.02 to 1.91	1.62	1.20 to 2.17
Model 3					
Parental exposure to solvents					
Only wife exposed	372	1.46	1.10 to 1.94	1.56	1.17 to 2.09
Only man exposed					
Monthly	453	1.26	0.93 to 1.72	1.32	0.97 to 1.82
Daily or weekly	131	1.51	0.97 to 2.35	1.46	0.92 to 2.30
Both parents exposed					
Man monthly exposed	308	1.42	1.01 to 1.98	1.65	1.17 to 2.33
Man daily or weekly exposed	77	1.99	1.17 to 3.37	2.10	1.22 to 3.60

*Logistic regression analyses. All the models include female age. Multivariate model adjusted for female and male BMI, female smoking, male use of alcohol, and state. A category of missing information was included in the models when necessary.

The association of solvent exposure and fertility was examined in a series of subset analyses to evaluate the robustness of our findings (fig 2). These included: (1) restriction of the study to wives who lived on a farm 10 years ago (to reduce potential exposure misclassification for women, n = 1075); (2) exclusion of women who were pregnant or breast feeding at the time of data collection (women are likely to reduce their smoking and probably also their exposure to chemicals during pregnancy and breast feeding, n = 1600); (3) stratifying according to age of female at start of pregnancy attempt (⩽30 years, n = 1093 *v* >30 years, n = 1019); (4) exclusion of subjects with a pregnancy attempt date within one year of data collection (to further balance the TTP starting time for subfertile and fertile subjects, n = 1809); and (5) stratifying on the state of residence (Iowa, n = 1651 or North Carolina, n = 461).

The association of female solvent exposure and subfertility was generally stable across different subset analyses (fig 2). Particularly strong associations were found for women who had lived on a farm 10 years ago, for older wives (>30 years), and women living in North Carolina. The relation between subfertility and male solvent exposure was less consistent than the association with female exposure. Compared to overall results, the association was weaker for men married to women who had lived on a farm 10 years ago, for the sample after excluding couples with a pregnancy attempt within a year of enrolment, for men whose wives were ⩾30 years, and for men living in North Carolina. The association between subfertility and solvent exposure to either parent was consistently seen across the different subset analyses. However, the association was attenuated in the subset of younger couples (wife ⩽30 years).

The association of solvent exposure and subfertility did not change when we limited analyses to participants with the more certain subfertility data by excluding those multigravid subfertile couples for whom fertility status was assessed on the basis of subfertility history and pregnancy interval (n = 1888, 224 exclusions). The adjusted OR for female exposure was 1.52 (95% CI 1.18 to 1.97), the ORs for low and high male exposure were 1.21 (95% CI 0.87 to 1.67) and 1.52 (95% CI 0.97 to 2.38), and the OR for exposure to either parent was 1.63 (95% CI 1.13 to 2.33).

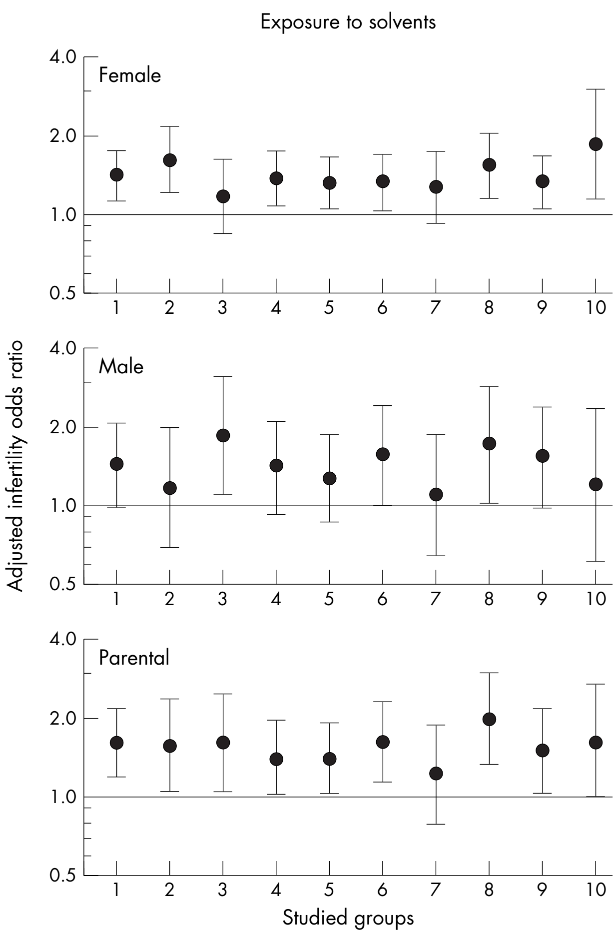

Figure 2 Sensitivity analyses of the association of solvents and subfertility among farm couples. The figures show adjusted subfertility odds ratios and 95% CIs. The sample sets are: 1 = entire analysis sample (n = 2112), 2 = wife lived on a farm 10 years ago (n = 1075), 3 = wife did not live on a farm 10 years ago (n = 1037), 4 = pregnant or breast feeding women excluded (n = 1600), 5 = TTP started one to four years ago (n = 1809), 6 = wife never smoked (n = 1548), 7 = wife ⩽30 years (n = 1093), 8 = wife >30 years (n = 1,019), 9 = state of residence is Iowa (n = 1651), 10 = state of residence is North Carolina (n = 461).

DISCUSSION

Our finding of reduced fertility among women with reported exposure to solvents is in accordance with the findings of several previous studies.[14–22] A few studies, however, have been negative.[23 24] The risk is difficult to attribute to specific solvents, because the studied solvents varied.

The evidence for males is less consistent. A few studies have shown a weak association,[17 25–27] but others have been negative.[14 20 23 28 29] Interestingly, a recent Dutch study of in vitro fertilisation (IVF) patients showed decreased implantation rates for women whose partners were exposed to organic solvents.[30] In the Agricultural Health Study, we see an association for both male and female solvent exposure, though the male effect is less consistent than the female effect across analyses of separate subsets of the population.

Our study has several strengths: (1) the study population is large and homogenous (licensed pesticide applicators in Iowa and North Carolina, all of whom were farmers); (2) exposure data were reported directly by men and women themselves rather by one of the partners as is sometimes the case in occupational studies, and information on exposures was collected independently of fertility information; (3) our study subjects are independent farmers who function as both management and labour, which increases the quality of information they can provide about farm activities and chemicals used; (4) periods of infertility that did not result in pregnancy were included (this is important because exclusion of unsuccessful attempts may mask a true effect[31]); and (5) the design used reduces the potential for time-trend bias.[13] In this study, the distribution of start of attempt times was similar for the fertile and subfertile subjects. This is critical because only information on current (or usual) solvent exposure was available.

Our study has some weaknesses that must be considered. Only categorical data on subfertility were available rather than actual time to pregnancy. This may make it more difficult to detect a true association. Exposure to solvents was based on self-reported work description, and no biological or environmental measures were available. Timing of exposure in relation to the start of attempt times could not be ascertained precisely. However, this type of exposure misclassification is likely to be non-differential, because the times of attempts are not expected to be differentially distributed by fertility status. Therefore, our findings may be biased towards unity. Moreover, we observed a strong association for women who had lived on a farm 10 years ago, but a weaker association for women who did not live on a farm 10 years ago. We think that this reflects potential for exposure misclassification. Depending on when these women moved to the farm, their current exposure patterns may not reflect exposure during their pregnancy attempt. To the extent that farm activities remain stable, the exposures at enrolment of women that lived on a farm 10 years ago would be more likely to reflect exposures throughout the four year study window.

Another source of potential exposure misclassification is related to the reproductive status of the wife. As expected, pregnant or breast feeding women at the time of interview were less often exposed to solvents than other women. Furthermore, we found that women who had preschool aged children at the time of data collection also were less likely to report exposure than did childless women or women who had older children. The opposite exposure pattern seemed to be true for men. Since farm tasks must be done regardless of family structure, it is likely that farm couples redistribute these tasks when family situations change. Thus, it is possible that applicators assume responsibility for chores previously done by the wife when she is pregnant or occupied by the care of small children. Because current pregnancy, breast feeding, or having young children reflect higher fertility, on average, it is likely that this type of differential exposure misclassification will bias the findings towards overestimation of the subfertility association for women and underestimation of the subfertility odds ratio for men. Therefore, we also assessed risk using a composite variable for combined parental exposure to solvents. Parental exposure to solvents was significantly related to subfertility and the effect was consistent across subsets of the population. The strongest association was seen in families where both parents were exposed to solvents. This adds to the evidence for adverse effects of solvent exposures on males as well as females.

The overall rate of subfertility was high in the analysis sample. This is expected because unsuccessful attempts to conceive were included (couples currently trying to conceive totalled 14% of the eligible subjects), and half the couples were over 30. In general, infertility rates are highly dependent on the definition of infertility. In a US study,[32] the prevalence of a history of infertility ranged from 6.1% (physician diagnosis) to 32.6% (unprotected intercourse for 12 months), the latter figure being similar to that in our study (28%). It was difficult to define fertility status in the case of multiple pregnancies because infertility history was not pregnancy specific. However, the findings were very similar when the analysis was restricted to those couples with the more certain subfertility data.

Data were available on many potential confounders and the findings remained after adjustment. However, the data on confounders were not collected to coincide with the start of the attempt time. This could introduce bias, especially for women, because women often change their habits when in different reproductive situations. Smoking data may show the most misclassification, as women are encouraged to stop smoking when pregnant or raising children. When we restricted the analysis to women who never smoked, however, the association with solvents was virtually unchanged. Therefore, misclassification of potential confounders may not be an important source of bias in the present study.

We have no explanation for the different findings between the states. For the variation by age, however, it is possible that that susceptibility to toxins increases with increasing age for both women and men.

The findings of our study provide further evidence that organic solvents can impair fertility. There is ample evidence that solvent exposure is associated with reduced female fertility, and women trying to conceive should avoid exposure. However, little is known about effects of specific solvents, hazardous exposure levels, and relevant exposure windows. Males may also be adversely affected, though the evidence for female effects is still stronger than for male effects.

Main messages

- The findings provide further evidence that use of solvents can impair female fertility.
- Males may also be adversely affected.
- Couples on farms often share work; current pregnancy or young children in household can influence who is exposed.

Policy implications

- Women and men trying to achieve conception should minimise solvent exposure.

ACKNOWLEDGEMENTS

We thank Stuart Long for assisting with data management, Clarice Weinberg for helpful discussions regarding misclassification in women with young children, and Allen Wilcox and Joanne Promislow for their comments on an earlier draft of the manuscript.

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Competing interests: none

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